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(54) Title: METHODS FOR TREATMENT OF CONDITIONS AFFECTED BY ACTIVITY OF MULTIDRUG TRANSPORTERS

(57) Abstract: One aspect of the present invention is a method of treating a condition or disease associated with the activity of a multidrug transporter protein comprising administering to a mammal with a condition or disease associated with the activity of a multidrug transporter protein an effective quantity of a purine derivative or analogue, a tetrahydroindolone derivative or analogue, or a pyrimidine derivative or analogue. If the compound is a purine derivative, the purine moiety can be guanine or hypoxanthine. A particularly preferred bifunctional purine derivative is N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide. Methods according to the present invention can be used to treat cancer, a microbial or parasitic infection, HIV, infection, or a condition associated with inflammation such as asthma or rheumatic disease.

METHODS FOR TREATMENT OF CONDITIONS AFFECTED BY ACTIVITY OF MULTIDRUG TRANSPORTERS

CROSS-REFERENCES

This application claims priority from Provisional Application Serial No. 60/216,616, filed July 7, 2000, by Eve M. Taylor, and entitled "Methods for Treatment of Conditions Affected by Activity of Multidrug Transporters," which is incorporated herein in its entirety by this reference.

BACKGROUND OF THE INVENTION

This invention is directed to methods for treatment of conditions affected by activity of multidrug transporters, particularly with purine derivatives or analogues, tetrahydroindolone derivatives or analogues, or pyrimidine derivatives or analogues.

Multidrug transporters are membrane proteins that are able to expel a broad range of toxic molecules from the cell. These multidrug transporters belong to the ATP-binding cassette (ABC) family of transport proteins that utilize the energy of ATP hydrolysis for activity.

Many cancers are intrinsically resistant to anticancer drugs or become resistant to chemotherapy after many rounds of treatment. A major mechanism of resistance of cancer cells to cancer drugs such as adriamycin, etoposide, vinblastine, actinomycin D, and taxol is the overexpression of the ABC transporters, P-glycoprotein and the Multidrug Resistance Associated Proteins (MRPs).

In microorganisms, multidrug transporters play an important role in conferring antibiotic resistance on pathogens. Homologues of human P-glycoprotein and MRP have been found in microorganisms and have been implicated in malaria drug resistance. Multidrug transporters found in bacteria are described in H.W. van Veen & W.I. Konings, "Multidrug Transporters from Bacteria to Man: Similarities in Structure and Function," Semin. Cancer Res. 8: 188-191 (1997).

MDR transporters are expressed in normal tissues including kidney, intestine, brain, liver, testes, and placenta. They function in the efflux of compounds from these organs and thus influence the absorption, the excretion, and the body distribution of drugs. For example, multidrug transporters have been shown to confer low brain penetration of antiviral compounds used to treat HIV reducing their efficacy in the treatment of AIDS-related neurodegeneration.

In addition to a role in the efflux of drugs, MRPs transport endogenous leukotriene C_4 (LTC_4). LTC_4 is an active component of the "slow reacting substance of anaphylaxis" and is implicated in the pathogenesis of inflammatory diseases such as asthma and rheumatic disease.

In addition to P-glycoprotein and MRPs, this class of transporters includes the lung-resistance protein (LRP) and the transporter of antigenic peptides (TAP). These transporters are described in the following references: M.M. Gottesman & I. Pastan, "Biochemistry of Multidrug Resistance Mediated by the Multidrug Transporter", Annu. Rev. Biochem. 63: 385-427 (1993); V. Ling, "Multidrug Resistance: Molecular Mechanisms and Clinical Relevance", Cancer Chemother. Pharmacol. 40 (Suppl): S3-S8 (1997); F.J. Sharom, "The P-Glycoprotein Efflux Pump: How Does It Transport Drugs?", J. Membrane Biol. 160: 161-175 (1997); A.F. List, "Non-P-Glycoprotein Drug Export Mechanisms of Multidrug Resistance", Semin. Hematol. 34 (Suppl. 5): 20-24 (1997); W.A. Banks, "Physiology and Pathology of the Blood-Brain Barrier: Implications for Microbial Pathogenesis, Drug Delivery and Neurodegenerative Disorders", J. Neurovirol. 5: 538-555 (1999); A. Lo & G.J. Burckart, "P-Glycoprotein and Drug Therapy in Organ Transplantation", J. Clin. Pharmacol. 39: 999-1005 (1999); and D. Lautier et al., "Multidrug Resistance Mediated by the Multidrug Resistance Protein (*MRP*) Gene",Biochem. Pharmacol. 52: 967-977 (1996); P. Borst, R. Evers, M. Kool & J. Wijnholds, "The multidrug resistance protein family", Biochim. Biophys. Acta 1461: 347-357.

Therefore, there exists a need for methods that can modulate or inhibit the activity of multidrug transporter proteins to enable improved treatment of cancer, infectious diseases, HIV infection, and inflammation, among other diseases and conditions in which the activity of multidrug transporter proteins is significant. Preferably, these methods should be able to be combined with methods that enable active compounds to pass through the blood-brain barrier, making combined therapy more efficient. These methods should also be suitable for use with a large variety of active compounds and should not depend on the specific interactions between each active compound and the transporter proteins.

SUMMARY

One embodiment of the present invention is a method of treating a condition or disease associated with the activity of a multi-drug transporter protein comprising

administering to a patient suffering from a condition or disease associated with the activity of a multi-drug transporter protein an effective quantity of a compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L though a carbonyl group wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having activity against a multi-drug transporter protein; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

The purine moiety can be selected from the group consisting of hypoxanthine and guanine, as well as other purine moieties. A number of purine derivatives suitable for use in methods according to the present invention are disclosed. A particularly preferred purine derivative is N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide. Preferably, the compound is capable of passing through the blood-brain barrier.

The multidrug transporter protein can be selected from the group consisting of P-glycoprotein and multidrug resistance associated proteins (MRPs).

The condition or disease associated with the activity of a multidrug transporter protein can be selected from the group consisting of cancer, a microbial or parasitic infection, HIV infection, and a condition associated with inflammation. The condition associated with inflammation can be asthma or rheumatic disease. (but are not limited to)

Another embodiment of the present invention is a method of increasing intestinal absorption of a drug transported by a multidrug transporter protein

comprising administering to a mammal an effective quantity of a bifunctional purine derivative capable of bypassing the blood-brain barrier as described above.

Yet another embodiment of the present invention is a method of improving the penetration of a drug transported by a multidrug transporter into the central nervous system comprising administering to a mammal an effective quantity of a compound as described above.

Still another embodiment of the present invention is a method of decreasing renal excretion or renal toxicity of a drug transported by a multidrug transporter protein comprising administering to a mammal an effective quantity of a compound as described above.

Yet another embodiment of the present invention is a method of treating a malignancy comprising:

(1) administering an effective quantity of an antineoplastic agent transported by a multidrug transporter protein to a mammal with cancer; and

(2) administering an effective quantity of a compound as described above.

In this method, the antineoplastic agent can be selected from the group consisting of adriamycin, etoposide, vinblastine, actinomycin D, and taxol.

Yet another embodiment of the present invention is a method for screening a compound for the existence or nonexistence of multidrug resistance transporter protein inhibitory activity comprising the steps of:

(1) adding the compound to a culture of cancer cells that constitutively express or are induced to express at least one multidrug resistance transporter protein;

(2) adding a cytotoxic agent transported by the multidrug resistance transport protein to the cells;

(3) determining the effect of the compound on the activity of the multidrug resistance transporter protein by performing one or both of a cytotoxicity assay and a drug accumulation assay on the cancer cells to measure either the cytotoxicity of the cytotoxic agent or the accumulation of the cytotoxic agent in the cancer cells; and

(4) comparing the effect of the compound on the activity of the multidrug transporter protein with the effect of a reference compound, N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide.

BRIEF DESCRIPTION OF THE DRAWINGS

The following invention will become better understood with reference to the specification, appended claims, and accompanying drawings, where:

Figure 1 is a set of graphs showing the efflux of ^{14}C-labeled N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide (AIT-082) and ^{3}H-labeled sucrose after intracerebroventricular (icv) administration: (a) graph showing time course; (b) bar graph showing $t_{1/2}$;

Figure 2 is a set of graphs showing the efflux of ^{14}C-labeled AIT-082 and ^{3}H-labeled sucrose after intraparenchymal (ipc) administration: (a) graph showing time course; (b) bar graph showing $t_{1/2}$;

Figure 3 is a graph showing the saturability of ^{14}C-labeled AIT-082 efflux;

Figure 4 is a graph showing the effect of inhibitors of P-gp and MRP on the efflux of ^{14}C-labeled AIT-082 after icv administration;

Figure 5 is a graph showing the effect of inhibitors of P-gp and MRP on the efflux of ^{14}C-labeled AIT-082 after ipc administration; and

Figure 6 is a graph showing the effect of AIT-082 on the efflux of ^{3}H-labeled quinidine after icv administration.

DESCRIPTION

We have discovered that the bifunctional purine derivative N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide (also known as AIT-082 and leteprinim potassium), which bypasses the blood-brain barrier and is transported into brain by a nonsaturable mechanism, is an inhibitor or modulator of the multidrug transporters P-glycoprotein and MRP. This property of inhibiting or modulating one or more of the multidrug transporters P-glycoprotein and MRP, therefore, should also be possessed by other purine derivatives and analogues, tetrahydroindolone derivatives and analogues, and pyrimidine derivatives and analogues that can pass through the blood-brain barrier, as discussed below.

Accordingly, one aspect of the present invention is a method of treating a condition or disease associated with the activity of a multidrug transporter protein comprising administering to a mammal with a condition or disease associated with the activity of a multidrug transporter protein an effective amount of a compound having activity against a multi-drug transporter protein, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a

tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L though a carbonyl group wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having activity against a multi-drug transporter protein; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

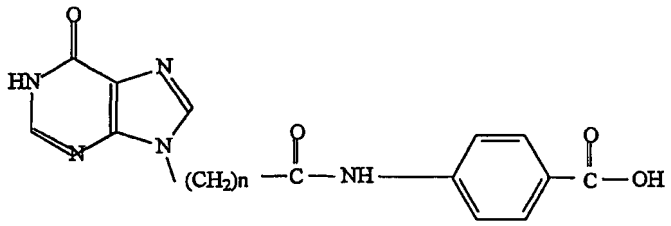
As used herein, the term "associated with" means either than the disease or condition directly affects the activity of a multidrug transporter protein, such as occurs in the overproduction of these proteins in cancer cells, or that, in the absence of inhibition of the multidrug transporter protein, the activity of the protein affects the treatment of the disease or condition such as by causing accelerated transport of a drug out of cells that are affected by the disease or condition.

Typically, a compound useful in a method of the present invention is capable of passing through the blood-brain barrier.

In one preferred embodiment of methods according to the present invention, the moiety A is a purine moiety.

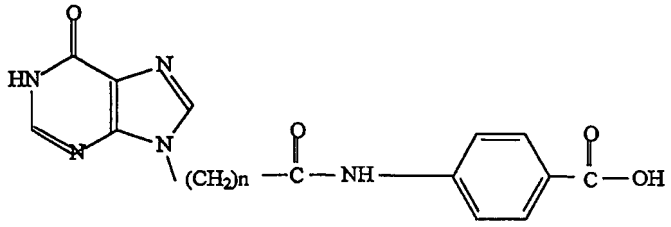
In one alternative, A is a substituted or unsubstituted hypoxanthine moiety. Typically, in this alternative, L has the structure $-(CH_2)_n-$ where n is an integer from 1 to 6.

The compound can be a compound of formula (I)



where n is an integer from 1 to 6 and R is hydrogen or lower alkyl or is a salt or prodrug ester of a compound of formula (I) wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl. Typically, the compound is a compound of formula (I) wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl. Typically, R is hydrogen, and the compound is N-4-[[3-(6-oxo-1,6-dihydropurin-9-yl)-1-oxopropyl] amino] benzoic acid, designated AIT-082. Alternatively, R is ethyl, and the compound is N-4-[[3-(6-oxo-1,6-dihydropurin-9-yl)-1-oxopropyl] amino] benzoic acid ethyl ester.

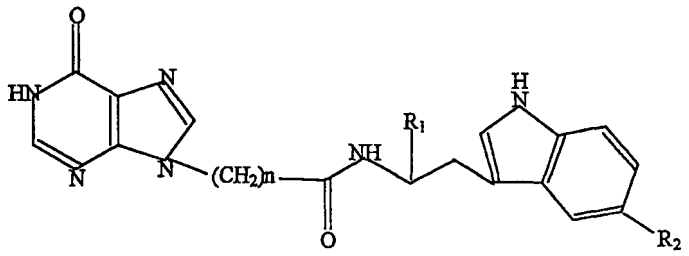
When the purine moiety is hypoxanthine, a preferred purine derivative is a compound of formula (I)



(I)

wherein n is an integer from 1 to 6 or of a salt or prodrug ester of formula (I) wherein n is an integer from 1 to 6. Typically, the purine derivative is a compound of formula (I) wherein n is an integer from 1 to 6. Preferably, n is 2 and the compound is N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide, also known as AIT-082. The activity of this compound is described further in the Example.

Alternatively, the purine derivative can be a 9-substituted hypoxanthine derivative of formula (II)

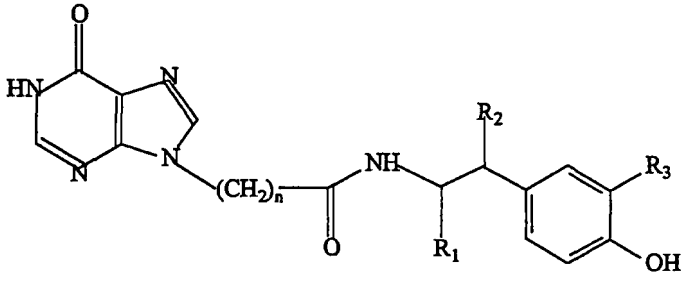


(II)

wherein n is a integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, where W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, and R_2 is selected from the group consisting of H and OH.

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H and R_2 is OH and the purine derivative is N-(2-(5-hydroxyindol-3-yl))ethyl-3-(6-oxohydropurine-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H and R_2 is H and the purine derivative is N-(2-indol-3-yl)ethyl-3-(6-oxohydropurin-9-yl) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, and R_2 is OH and the purine derivative is N-(1-carboxyl-(2-(5-hydroxyindol-3-yl))ethyl-3-(6-oxohydropurin-9-yl) propanamide.

As another alternative, the purine derivative can be a 9-substituted hypoxanthine derivative of formula (III)



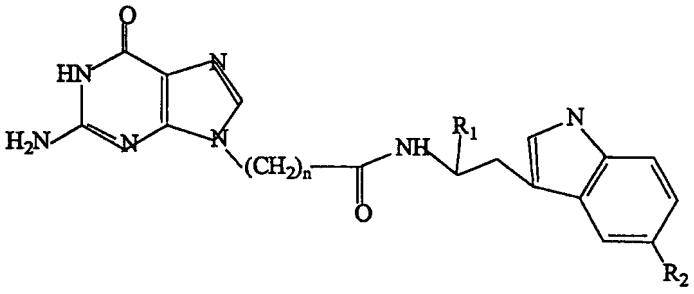
(III)

wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting of H and OH.

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H, R_2 is H, and R_3 is OH, and the purine derivative is N-(2-(3,4-dihydroxyphenyl))ethyl-3-

(6-oxohydropurin-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H, R_2 is OH, and R_3 is OH, and the purine derivative is N-(2-hydroxy-2-(3,4-dihydroxyphenyl))ethyl-3-(6-oxohydropurin-9-yl) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, R_2 is H, and R_3 is OH, and the purine derivative is N-(1-carboxyl-2-(3,4-dihydroxyphenyl))ethyl-3-(6-oxohydropurin-9-yl) propanamide.

When the purine moiety is guanine, one preferred purine derivative is a 9-substituted guanine derivative of formula (IV)

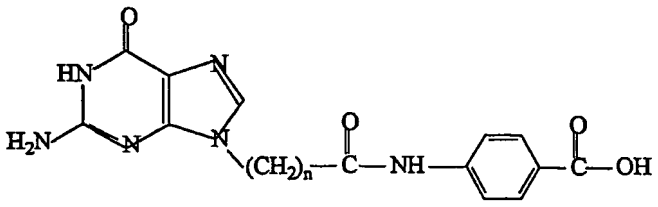


(IV)

wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, or W_1 is lower alkyl, amino, or lower alkylamino, and R_2 is selected from the group consisting of H and OH.

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H, and R_2 is OH, and the purine derivative is N-(2-(5-hydroxindol-3-yl))ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H, and R_2 is H and the purine derivative is N-(2-(2-indol-3-yl)ethyl))-3-(2-amino-6-oxohydropurin-9-yl)) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, and R_2 is OH, and the purine derivative is N-(1-carboxyl)-(2-(5-hydroxyindol-3-yl))ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

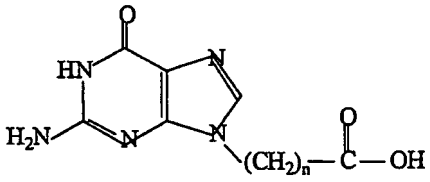
Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (V) wherein n is an integer from 1 to 6.



(V)

In this alternative, for one particularly preferred purine derivative, n is 2 and the compound is N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

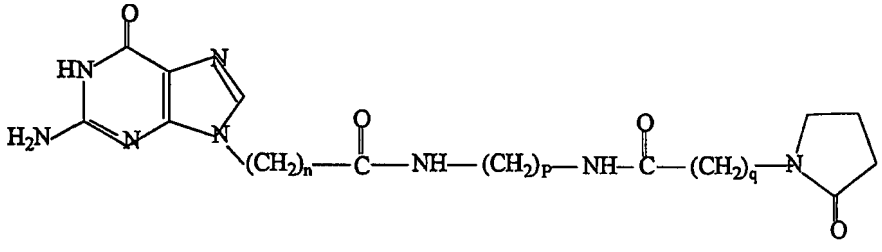
Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (VI) wherein n is an integer from 1 to 6.



(VI)

In this alternative, for one particularly preferred purine derivative, n is 2 and the compound is 3-(2-amino-6-oxohydropurine-9-yl) propanoric acid.

Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (VII) wherein n is an in integer from 1 to 6, p is an integer from 1 to 6, and q is an integer from 1 to 3.

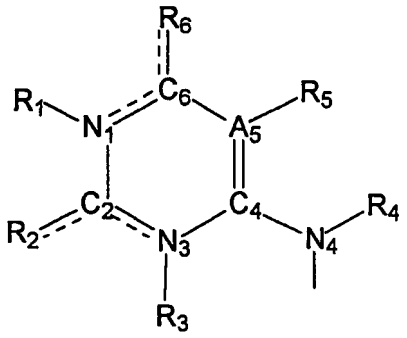


(VII)

In this alternative, for one particularly preferred purine derivative, n is 2, p is 2, and q is 1, and the purine derivative is N-[2-[[2-(2-oxopyrrolidin-1-yl)-1-oxoethyl]amino]ethyl] propanamide.

Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (VIII) wherein R_1 is selected from the group consisting of H, COOH, and $COOW_1$, where W_1 is selected from the group consisting of lower alkyl, amino, and

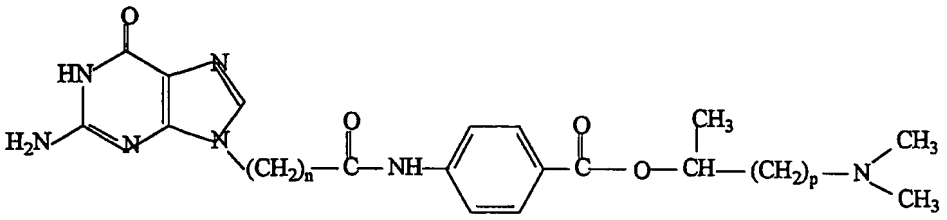
lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting of H and OH.



(VIII)

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H, R_2 is H, and R_3 is OH, and the purine derivative is N-(2-(3,4-dihydroxyphenyl)ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H, R_2 is OH, and R_3 is OH, and the purine derivative is N-(2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, R_2 is H, and R_3 is H and the compound is N-(1-carboxyl-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (IX) wherein n is an integer from 1 to 6 and p is an integer from 1 to 3.

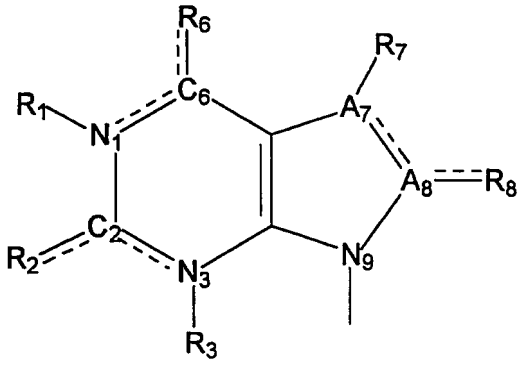


(IX)

In this alternative, for one particularly preferred purine derivative, n is 2, p is 1, and the compound is the 1-(dimethylamino)-2-propyl ester of N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

Other bifunctional hypoxanthine derivatives suitable for use in methods according to the present invention are disclosed in U.S. Patent No. 5,091,432 to Glasky, incorporated herein by this reference. Other bifunctional guanine derivatives suitable for use in methods according to the present invention are disclosed in U.S. Patent Application No. 09/419,153, by Glasky et al., incorporated herein by this reference.

More generally, purine-based compounds suitable for use in methods according to the present invention are compounds in which A is a substituted or unsubstituted 9-atom bicyclic moiety in which the 5-membered ring has 1 to 3 nitrogen atoms, the bicyclic moiety having the structure of formula (X)



(X)

where:

(1) if the bond between N_1 and the bond between C_5 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(2) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(3) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(4) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(5) A_7 and A_8 are C or N;

(a) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a single bond, then the bond between A_8 and R_8 is two single bonds to two hydrogen atoms or is a double bond in which R_8 is O or S and R_7 is two hydrogen atoms;

(b) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a double bond, then R_7 is hydrogen, the bond between A_8 and R_8 is a single bond and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(c) if A_7 and A_8 are both N, then the bond between A_7 and A_8 is a double bond, and R_7 and R_8 are not present;

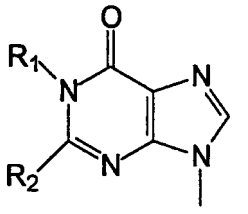
(d) if A_7 is C and A_8 is N, then the bond between A_7 and A_8 is a double bond, R_7 is hydrogen, and R_8 is not present;

(e) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a double bond, then R_7 is not present, the bond between A_8 is a single bond, and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(f) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a single bond, then R_7 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, the bond between A_8 and R_8 is a double bond, and R_8 is O or S; and

(6) N_9 is bonded to L; with the proviso that A does not have the structure of an unsubstituted guanine or hypoxanthine.

The purine moiety can be a purine moiety of formula (XI)



(XI)

in which:

(1) R_1 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, and heteroaralkyl; and

(2) R_2 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylokoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroarylkylaminocarbonyl in which the alkyl portions could be cyclic and can contain from one to three heteroatoms which could be N, O, or S, with the proviso that both R_1 and R_2 are not hydrogen and that R_1 is not hydrogen when R_2 is amino.

The purine moiety of formula (XI) is a hypoxanthine or a guanine derivative but excludes unsubstituted hypoxanthine, in which R_1 and R_2 are hydrogen, and unsubstituted guanine, in which R_1 is hydrogen and R_2 is amino.

In one particularly preferred embodiment, R_1 is butyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is benzyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is dimethylaminoethyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is cyclopentyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is cyclohexylmethyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is cyclopropylmethyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is hydrogen and R_2 is phenyl.

In another preferred embodiment, R_1 is hydrogen and R_2 is trifluoromethyl.

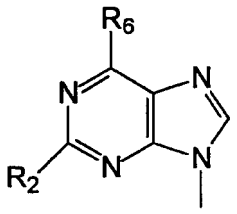
In another preferred embodiment, R_1 is hydrogen and R_2 is butyl.

In another preferred embodiment, R_1 is butyl and R_2 is butyl.

In another preferred embodiment, R_1 is hydrogen and R_2 is methyl.

In another preferred embodiment, R_1 is hydrogen and R_2 is phenylamino.

Alternatively, the purine moiety can be a purine moiety of Formula (XII)



(XII)

in which:

(1) R_2 is selected from the group consisting of hydrogen, halo, amino, OQ_3, SQ_3, $NHNH_2$, $NHOQ_3$, NQ_3Q_4, or NHQ_3, where Q_3 and Q_4 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_3 and Q_4 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3 where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(2) R_6 is selected from the group consisting of hydrogen, halo, amino,

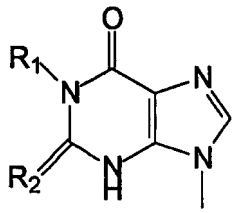
OQ_5, SQ_5, $NHNH_2$, $NHOQ_5$, NQ_5Q_6, or NHQ_6, where Q_5 and Q_6 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_5 and Q_6 are present together and are alkyl, they can be taken together to form a 5- or 6- membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

In one preferred example of this embodiment, R_2 is hydrogen and R_6 is $-NH_2$ or $-N(CH_3)_2$.

In another preferred example of this embodiment, R_2 is hydrogen and R_6 is Cl.

In yet another preferred example of this embodiment, R_2 is $-NH_2$ and R_6 is Cl.

In another alternative, the purine moiety is the purine moiety of Formula (XIII)



in which:

(1) R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl; and

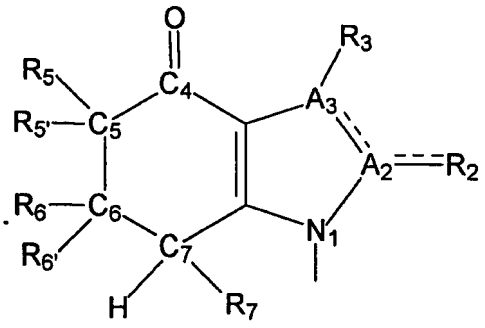
(2) R_2 is O or S.

Preferably, in this embodiment, R_1 is hydrogen and R_2 is O or S.

Particularly preferred purine-based compounds for use in methods according to the present invention include: (1) 4-[3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (2) 4-[3-(1-butyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (3) 4-[3-(1-methyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (4) 4-[3-(1-(2-dimethylaminoethyl)-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (5) 4-[3-(2,6-dioxo-

1,2,3,6-tetrahydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (6) 4-[3-(6-methoxypurin-9-yl)propionylamino] benzoic acid ethyl ester; (7) 4-[3-(6-dimethylaminopurin-9-yl)propionylamino] benzoic acid ethyl ester; (8) 4-[3-(2-amino-6-chloropurin-9-yl)propionylamino] benzoic acid ethyl ester; (9) 4-[2-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl)propionylamino]benzoic acid ethyl ester; (10) 4-[2-(2-butyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino]benzoic acid ethyl ester; (11) 4-[2-(6-oxo-2-phenyl-1,6-dihydropurin-9-yl)propionylamino]benzoic acid ethyl ester; (12) 4-{[3-(6-chloropurin-9-yl)propionyl]methylamino} benzoic acid methyl ester; (13) 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-[3-(2-oxopyrrolidin-1-yl)propyl] propionamide; (14) 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-{2-[2-(2-oxopyrrolidin-1-yl)acetylamino]ethyl} propionamide; (15) N-3-(2-oxopyrrolidin-1-yl)propyl]-3-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl) propionamide; and (16) 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-(3-morpholin-4-yl-propyl) propionamide.

In another alternative of methods according to the present invention, the compound is a tetrahydroindolone derivative or analogue where A is a 9-atom bicyclic moiety in which the 5-membered ring has one to three nitrogen atoms, the bicyclic moiety having the structure of formula (XIV)



(XIV)

where:

(1) N_1 is bonded to L;

(2) A_2 and A_3 are C or N;

(a) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a single bond, then the bond between A_2 and R_2 is two single bonds, two hydrogen atoms or is a double bond in which R_2 is O or S and R_3 is two hydrogen atoms;

(b) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a double bond, then R_3 is hydrogen, the bond between A_2 and R_2 is a single bond and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(c) If A_2 and A_3 are both N, then the bond between A_2 and A_3 is a double bond and R_2 and R_3 are not present;

(d) If A_2 is N and A_3 is C, then the bond between A_2 and A_3 is a double bond, R_2 is not present, and R_3 is hydrogen;

(e) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a double bond, then R_3 is not present, the bond between A_2 and R_2 is a single bond, and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(f) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a single bond, then R_3 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkenyl, the bond between A_2 and R_2 is a double bond, and A_2 is O or S;

(3) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHQ_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(4) $R_{5'}$ is hydrogen unless R_5 is alkyl, in which case R_5 is hydrogen or the same alkyl as R_5;

(5) R_5 and $R_{5'}$ can be taken together as a double bond to C_5, and can

be O, S, NQ_3, or C which can be substituted with one or two groups R_5, where Q_3 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

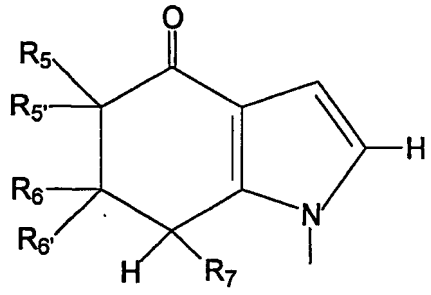
(6) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, NH_2, NHQ_4, NQ_4Q_5, OH, OQ_4, or SQ_4, where Q_4 and Q_5 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_4 and Q_5 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(7) $R_{6'}$ is hydrogen unless R_6 is alkyl, in which case $R_{6'}$ is hydrogen or the same alkyl as R_6;

(8) R_6 and $R_{6'}$ can be taken together as a double bond to C_6 and can be O, S, NQ_6, or C which can be substituted with one or two groups R_5, and where Q_6 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(9) R_7 is hydrogen unless R_5 is alkyl and $R_{5'}$ is hydrogen, in which case R_7 is the same alkyl as R_5.

Typically, A is a tetrahydroindolone moiety. More typically, the tetrahydroindolone moiety is a tetrahydroindolone moiety of formula (XV)



(XV)

in which:

(1) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NH_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

(2) $R_{5'}$ is hydrogen;

(3) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHW_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S and where W_1 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

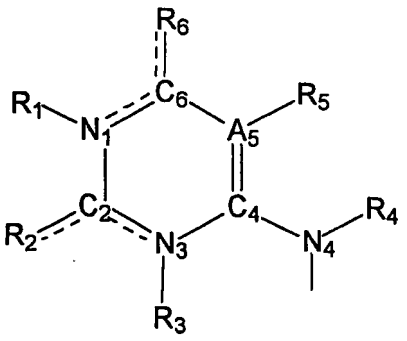
(4) $R_{6'}$ is hydrogen; and

(5) R_7 is hydrogen.

Typically, R_5, $R_{5'}$, R_6, $R_{6'}$, and R_7 are all hydrogen.

When A is a tetrahydroindolone moiety, preferred compounds are 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid ethyl ester and 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid.

In another alternative, the compound is a pyrimidine derivative or pyrimidine analogue. In this alternative, A is is an amino-substituted 6-membered heterocyclic moiety of formula (XVI)



(XVI)

where:

(1) if the bond between N_1 and the bond between C_6 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(2) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(3) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(4) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 and R_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl,

heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3, where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(5) R_4 is hydrogen, alkyl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl;

(6) A_5 is carbon or nitrogen;

(7) if A_5 is nitrogen, then R_5 is not present;

(8) if A_5 is carbon, then R_5 is hydrogen, amino, alkyl, alkoxy, halo, nitro, aryl, cyano, alkenyl, or alkaryl;

(9) if R_5 and R_6 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(10) N_4 is bonded to L.

Typically, A_5 is carbon and the 6-membered heterocyclic moiety is a pyrimidine moiety.

When A is a pyrimidine moiety, in one alternative, R_2 is O and R_3 is hydrogen. In this alternative, the pyrimidine moiety can be cytosine, thymine, uracil, 3-methyluracil, 3-methylthymine, 4-methylcytosine, 5-methylcytosine, 5-hydroxymethylcytosine, 5-hydroxyuracil, 5-carboxymethyluracil, or 5-hydroxymethyluracil.

In another alternative, R_2 is S and R_3 is hydrogen. In this alternative, the pyrimidine moiety can be 2-thiouracil, 5-methylamino-2-thiouracil, 5-methyl-2-thiouracil, or 2-thiocytosine.

In still another alternative, R_2 is amino and the bond between C_2 and N_3 is a double bond. In this alternative, the pyrimidine moiety can be 2-aminopyrimidinone or 2-amino-4-chloropyrimidine.

In still another alternative, R_2 is hydrogen and the bond between C_2 and N_3 is a double bond. In this alternative, the pyrimidine moiety can be 4-chloropyrimidine, 5-amino-4-chloropyrimidine, 4-chloro-5-methylpyrimidine, 4-chloro-5-hydroxymethylpyrimidine, or 4-chloro-5-carboxymethylpyrimidine.

In still another alternative, R_1 is hydrogen, methyl, or ethyl, R_5 is hydrogen, methyl, or ethyl, and R_6 is O. In this alternative, the pyrimidine moiety can be pyrimidinone.

Particularly preferred pyrimidine compounds include: 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; and 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

In accordance with the present invention, and as used herein, the following terms, when appearing alone or as part of a moiety including other atoms or groups, are defined with the following meanings, unless explicitly stated otherwise. In

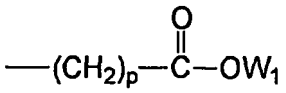
addition, all groups described herein can be optionally substituted unless such substitution is excluded. The term "alkyl," as used herein at all occurrences, refers to saturated aliphatic groups including straight-chain, branched-chain, and cyclic groups, all of which can be optionally substituted. Preferred alkyl groups contain 1 to 10 carbon atoms. Suitable alkyl groups include methyl, ethyl, and the like, and can be optionally substituted. The term "alkenyl," as used herein at all occurrences, refers to unsaturated groups which contain at least one carbon-carbon double bond and includes straight-chain, branched-chain, and cyclic groups, all of which can be optionally substituted. Preferable alkenyl groups have 2 to 10 carbon atoms. The term "alkoxy" refers to the ether –O—alkyl, where alkyl is defined as as above. The term "aryl" refers to aromatic groups which have at least one ring having a conjugated π-electron system and includes carbocyclic aryl and biaryl, both of which may be optionally substituted. Preferred aryl groups have 6 to 10 carbon atoms. The term "aralkyl" refers to an alkyl group substituted with an aryl group. Suitable aralkyl groups include benzyl and the like; these groups can be optionally substituted. The term "aralkenyl" refers to an alkenyl group substituted with an aryl group. The term "heteroaryl" refers to carbon-containing 5-14 membered cyclic unsaturated radicals containing one, two, three, or four O, N, or S heteroatoms and having 6, 10, or 14 π-electrons delocalized in one or more rings, e.g., pyridine, oxazole, indole, thiazole, isoxazole, pyrazole, pyrrole, each of which can be optionally substituted as discussed above. The term "sulfonyl" refers to the group -$S(O_2)$-. The term "alkanoyl" refers to the group -C(O)Rg, where Rg is alkyl. The term "aroyl" refers to the group -C(O)Rg, where Rg is aryl. Similar compound radicals involving a carbonyl group and other groups are defined by analogy. The term "aminocarbonyl" refers to the group –NHC(O)-. The term "oxycarbonyl" refers to the group –OC(O)-. The term "heteroaralkyl" refers to an alkyl group substituted with a heteroaryl group. Similarly, the term "heteroaralkenyl" refers to an alkenyl group substituted with a heteroaryl group. As used herein, the term "lower," in reference to an alkyl or the alkyl portion of an another group including alkyl, is defined as a group containing one to six carbon atoms. The term "optionally substituted" refers to one or more substituents that can be lower alkyl, aryl, amino, hydroxy, lower alkoxy, aryloxy, lower alkylamino, arylamino, lower alkylthio, arylthio, or oxo, in some cases, other groups can be included, such as cyano, acetoxy, or halo. The term "halo" refers generally to fluoro, chloro, bromo, or iodo; more typically, "halo" refers to chloro.

As indicated above, the linker L is a hydrocarbyl moiety of 1 to 6 carbon atoms that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo. Preferably, the linker L has the structure $-(CH_2)_n-$ wherein n is an integer from 1 to 6. As detailed below, for most preferred embodiments of compounds useful in methods according to the present invention, a preferred linker has n equal to 2 or 3.

The moiety B is either: (i) –OZ, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; or (ii) $N(Y_1)$-D, where D is a moiety that promotes absorption of the compound, and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, which, when taken with D, can form a cyclic 5- or 6-membered saturated ring which can contain one other heteroatom which can be O, N, or S, of which N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S. Typically, Y_1 is hydrogen. Where the moiety B is –OZ, the moiety B is a carboxylic acid or carboxylic acid or ester. Typically, where B is a carboxylic acid ester, the moiety Z is a lower alkyl, such as methyl, ethyl, butyl, propyl, or isopropyl.

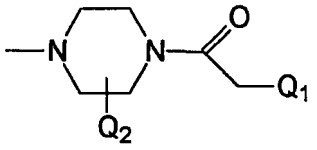
In one alternative, the moiety D, as described above, is a moiety having at least one polar, charged, or hydrogen-bond-forming group to improve the metabolic and bioavailability properties of the compound. The moiety D can be, but is not limited to, a moiety with physiological or biological activity such as nootropic activity. In one alternative, the moiety D can be a moiety containing at least one carboxyl, carboxamide, carboxyl ester, or carbonyl function. In another alternative, the moiety D can be a moiety containing at least one hydroxyl, primary amino, secondary amino, tertiary amino, sulfhydryl, or sulfonamidyl function. The moiety D can be cyclic or acyclic. Preferred examples of the moiety D are described below.

When the moiety D is a cyclic or acyclic moiety containing at least one carbonyl, carboxamide, carboxyl ester, or carbonyl function, in one preferred example, D is a carboxylic acid or carboxylic acid ester with the structure



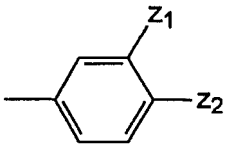
wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of hydrogen and lower alkyl. Typically, if W_1 is lower alkyl, it is methyl, ethyl, propyl, butyl, or isobutyl. Typically, p is 3. Typically, W_1 is hydrogen or ethyl.

In another preferred example, D and Y_1 are taken together to form a piperazine derivative as described in D. Manetti et al., "Molecular Simplification of 1,4-Diazabicyclo[4.3.0]nonan-9-ones Gives Piperazine Derivatives That Maintain High Nootropic Activity," J. Med. Chem. 43: 4499-4507 ("Manetti et al. (2000)"). B is an analogue of structure



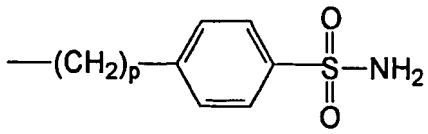
wherein Q_1 is hydrogen, methyl, ethyl, butyl, or propyl, Q_2 is hydrogen or methyl, where, if Q_2 is methyl, it can be located at either of the two possible positions in the piperazine ring.

In another preferred example, D has the structure



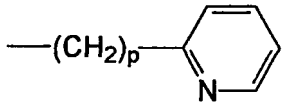
where one of Z_1 and Z_2 is hydrogen, and the other of Z_1 and Z_2 is –COOH or -$COOW_1$, wherein W_1 is alkyl. Typically, W_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, and isobutyl. Either of Z_1 or Z_2 can be hydrogen. When Z_1 is hydrogen and Z_2 is –COOH, the moiety B is *p*-aminobenzoic acid (PABA). When Z_1 is –COOH and Z_2 is hydrogen, the moiety B is *m*-aminobenzoic acid (MABA). When Z_1 is hydrogen and Z_2 is –$COOW_1$, the moiety B is an ester of *p*-aminobenzoic acid (PABA). When Z_1 is –$COOW_1$ and Z_2 is hydrogen, the moiety B is an ester of *m*-aminobenzoic acid (MABA). Typically, these esters are ethyl esters.

When the moiety D is a moiety that contains at least one hydroxyl, primary amino, secondary amino, tertiary amino, sulfhydryl, or sufonamidyl function, in one preferred example, D is a phenylsulfonamidyl moiety of structure



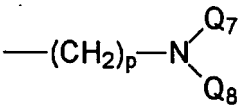
wherein p is an integer from 0 to 6. Typically, p is 2.

In another preferred example, D is an alkylpyridyl moiety of structure



wherein p is an integer from 1 to 6. Typically, p is 1.

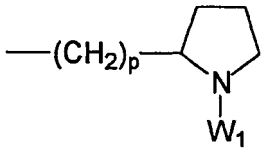
In another preferred example, D is a dialkylaminoalkyl moiety of the structure



wherein p is an integer from 1 to 6 and Q_7 and Q_8 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5 or 6 member ring which may contain 1 other heteroatom which can be N, O, or S, of which the N may be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

Where Q_7 and Q_8 can be taken together to form a five or six member ring, the ring is typically pyrrolidine, piperidine, or morpholine. The pyrrolidine ring can be optionally substituted with oxo. The piperidine ring can be optionally substituted with methyl or ethyl. Typically, p is 2 or 3.

In another preferred example, D is an alkylpyrrolidine moiety of the structure



wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of methyl, ethyl, and propyl. Typically, W_1 is methyl. Typically, p is 2.

Preferably, a compound useful in methods according to the present invention has a log P of from about 1 to about 4 in order to optimize bioavailability and CNS penetration of the compound.

The multidrug transporter protein to be inhibited can be selected from the group consisting of P-glycoprotein and multidrug resistance associated proteins (MRPs).

In methods according to the present invention, the disease or condition to be treated can be a malignancy, a microbial or parasitic infection, HIV infection, or a condition associated with inflammation. Multidrug transporters are found in bacteria and are associated with drug resistance, as described in H.W. van Veen & W.I. Konings, "Multidrug Transporters from Bacteria to Man: Similarities in Structure and Function," Semin. Cancer Res. 8: 188-191 (1997). The condition associated with inflammation can be asthma or a rheumatic disease.

Another aspect of the present invention is a method of increasing intestinal absorption of a drug transported by a multidrug transporter protein comprising administering to a mammal an effective quantity of a compound as described above.

Yet another aspect of the present invention is a method of improving the penetration of a drug transported by a multidrug transporter into the central nervous system comprising administering to a mammal an effective quantity of a compound as described above.

Yet another aspect of the present invention is a method of decreasing renal excretion or renal toxicity of a drug transported by a multidrug transporter protein comprising administering to a mammal an effective quantity of a compound as described above.

Yet another aspect of the present invention is a method of treating a malignancy comprising:

(a) administering an effective quantity of an antineoplastic agent transported by a multidrug transporter protein to a mammal with cancer; and

(b) administering an effective quantity of a compound as described above.

The antineoplastic agent can be selected from the group consisting of adriamycin, etoposide, vinblastine, actinomycin D, and taxol.

Exemplary studies and treatments were performed as discussed below using various dosages and routes of administration of selected exemplary compounds

representative of compositions that are effective with the methods of the present invention. Of course, those skilled in the art will recognize that the present invention is not specifically limited to the particular compositions, dosages or routes of administration detailed below.

Depending upon the particular needs of the individual subject involved, the compositions used in the present invention may be administered in various doses to provide effective treatment concentrations based upon the teachings of the present invention. What constitutes an effective amount of the selected composition will vary based upon such factors including the activity of the selected purine derivative, the physiological characteristics of the subject, the extent and nature of the subject's disease or condition and the method of administration. Exemplary treatment concentrations which have proven effective in modifying neural activity range from less than 1 μM to concentrations of 500 mM or more. Generally, initial doses will be modified to determine the optimum dosage for treatment of the particular mammalian subject. The compositions may be administered using a number of different routes including orally, topically, transdermally, intraperitoneal injection or intravenous injection directly into the bloodstream. Of course, effective amounts of the compounds may also be administered through injection into the cerebrospinal fluid or infusion directly into the brain, if desired.

The methods of the present invention may be effected using compounds administered to a mammalian subject either alone or in combination as a pharmaceutical formulation. Further, the compounds may be combined with pharmaceutically acceptable excipients and carrier materials such as inert solid diluents, aqueous solutions or non-toxic organic solvents. If desired, these pharmaceutical formulations may also contain preservatives and stabilizing agents and the like, as well as minor amounts of auxiliary substances such as wetting or emulsifying agents, as well as pH buffering agents and the like which enhance the effectiveness of the active ingredient. The pharmaceutically acceptable carrier can be chosen from those generally known in the art, including, but not limited to, human serum albumin, ion exchangers, dextrose, alumina, lecithin, buffer substances such as phosphate, glycine, sorbic acid, potassium sorbate, propylene glycol, polyethylene glycol, and salts or electrolytes such as protamine sulfate, sodium chloride, or potassium chloride. Other carriers can be used.

Liquid compositions can also contain liquid phases either in addition to or to the exclusion of water. Examples of such additional liquid phases are glycerin, vegetable oils such as cottonseed oil, organic esters such as ethyl oleate, and water-oil emulsions.

The compositions can be made into aerosol formations (i.e., they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichloromethane, propane, or nitrogen. Other suitable propellants are known in the art.

Formulations suitable for parenteral administration, such as, for example, by intravenous, intramuscular, intradermal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions. These can contain antioxidants, buffers, preservatives, bacteriostatic agents, and solutes that render the formulation isotonic with the blood of the particular recipient. Alternatively, these formulations can be aqueous or non-aqueous sterile suspensions that can include suspending agents, thickening agents, solubilizers, stabilizers, and preservatives. Compositions suitable for use in methods according to the present invention can be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically, or intrathecally. Formulations of compounds suitable for use in methods according to the present invention can be presented in unit-dose or multi-dose sealed containers, in physical forms such as ampules or vials.

Yet another aspect of the present invention is a screening method to identify compounds capable of inhibiting or modulating the activity of at least one multidrug transporter protein. This method comprises:

(1) adding the compound to a culture of cancer cells that constitutively express or are induced to express at least one multidrug resistance transporter protein;

(2) adding a cytotoxic agent transported by the multidrug resistance transport protein to the cells;

(3) determining the effect of the compound on the activity of the multidrug resistance transporter protein by performing one or both of a cytotoxicity assay and a drug accumulation assay on the cancer cells to measure either the cytotoxicity of the cytotoxic agent or the accumulation of the cytotoxic agent in the cancer cells; and

(4) comparing the effect of the compound on the activity of the multidrug

transporter protein with the effect of a reference compound, N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide.

The invention is illustrated by the following Example. This Example is presented for illustration only and is not intended to limit the invention.

Example

Involvement of Multidrug Resistance Transporters in Transport of the Bifunctional Purine Derivative N-4-Carboxyphenyl-3-(6-Oxohydropurin-9-yl) Propanamide out of Brain

AIT-082 (NEOTROFIN™, leteprinim potassium), a hypoxanthine derivative, has robust neurotrophic and neuroprotective actions *in vitro* and *in vivo* (reviewed by Rathbone et al., 1999), and is currently under investigation as a possible therapy for humans with mild to moderate Alzheimer's disease (Targum et al., 1999).

Previously, it was demonstrated that AIT-082 is transported into brain by a non-saturable mechanism and, using capillary depletion and microdialysis, it was demonstrated that AIT-082 is detectable in cortical extracellular fluid in low micromolar quantities (Taylor et al., 2000). Additionally, it was demonstrated that, after intracerebroventricular administration, ^{14}C-AIT-082 was transported out of brain with a $t_{½}$ of approximately 20 minutes. The rate of disappearance from brain was too rapid to be accounted for by passive mechanisms and, indeed, we demonstrated that the efflux of ^{14}C-AIT-082 from brain was inhibited by excess unlabeled AIT-082 (Taylor et al., 2000). These data suggested that AIT-082 was transported out of brain by a saturable mechanism.

The blood-brain barrier, which creates and maintains the privileged environment of the CNS, comprises three "lines of defense". The first is a physical barrier formed by tight junctions between endothelial cells of the brain capillaries and epithelial cells of the choroid plexus. Secondly, an enrichment of enzymes including peptidases and drug metabolizing enzymes creates an enzymatic barrier. The third level of protection consists of a collection of transporters that serve to transport compounds from brain to blood. Such transporters include the multidrug transporters, P-glycoprotein (P-gp) and multidrug resistance associated proteins (MRPs) (Banks et al., 1994).

Both P-gp (Cordon-Cardo et al., 1990; Sugawara et al., 1990; Hegmann et al., 1992; Jette et al., 1993; Rao et al., 1999) and MRP (Kusuhara et al., 1998; Regina et al., 1998; Huai-Yun et al., 1998; Gutmann et al., 1999; Nishino et al., 1999; Rao et al.,

1999; Seetharaman et al., 1998) are expressed in brain capillary endothelial cells and choroid plexus epithelial cells. The most compelling evidence for the role of the multidrug resistance proteins in blood-brain barrier function has come from gene knockout studies. MDR1a knockout mice, which lack P-gp, show increased blood-brain barrier permeability to digoxin, cyclosporin A, dexamethasone, vinblastine, ondansetron and loperamide and increased sensitivity to the neurotoxic effects of ivermectin (Schinkel et al., 1994, 1995, 1996, 1998). Furthermore, P-gp and MRP inhibitors have been shown to enhance the blood-brain barrier penetration of drugs including dideoxyinosine (DDI) (Galinsky et al., 1991), zidovudine (AZT) (Takasawa et al., 1997), cyclosporin A (Didier et al., 1995; Tsujui et al., 1993), quinidine (Kusuhara et al., 1997), colchicine (Drion et al., 1996) and vinblastine (Drion et al., 1996).

The substrate specificity of the P-gp and MRP transporters is broad. P-glycoprotein traditionally transports hydrophobic cationic or neutral compounds (Gottesman et al., 1996), however it has been shown to transport hydrophilic acids such as methotrexate (De Graaf et al., 1996). The MRPs are known to transport organic anions, glutathione conjugates, and peptidyl leukotrienes (Barrand et al., 1997). AIT-082 is a small organic molecule that contains a single aromatic carboxylate anion. These characteristics make AIT-082 a potential substrate for both P-gp and MRP and in this study we have investigated the role of these transporters in the saturable efflux of AIT-082 from brain.

Methods

Animals

Male Swiss-Webster CFW mice were supplied by Charles River Laboratories (Hollister, CA) and all experiments were conducted according to the NIH Guide on Care and Use of Laboratory Animals. Mice were 2-3 months old at the time of use.

Materials

AIT-082 (99.5% pure) was synthesized by Eprova (Schaffhausen, Switzerland) and ^{14}C-AIT-082 (51.5 mCi/mmol; ≥98% pure) was synthesized by Chemsyn Laboratories (Lenexa, Kansas, USA). ^{3}H-sucrose (5-15 Ci/mmol) was purchased from Amersham Pharmacia Biotech (Arlington Heights, IL) and ^{3}H-quinidine (10-20 Ci/mmol) was from American Radiolabeled Chemicals (St. Louis, MO). Probenecid and verapamil hydrochloride were purchased from Sigma Chemical Company (St. Louis, MO). MK-571 was purchased from Alexis Biochemicals (San Diego, CA).

Intracerebroventricular (icv) Efflux Experiments

These experiments were conducted according to the method of Banks et al. (1997) with minor modifications. The skull was exposed and, with a guarded 25 g needle, a hole was made through the skull at 1 mm anterior posterior (AP) and 1 mm lateral left (LL), relative to Bregma, and 3.5 mm dorsal ventral (DV), with respect to the skull. A guarded 1 μL Hamilton syringe (25g) was used to inject 1 μL of PBS containing ^{14}C-AIT-082 (~4.5x10^4 dpm/μL), ^{3}H-sucrose (~3x10^4 dpm/μL), or ^{3}H-quinidine (~3x10^4 dpm/μL) icv into mice. After injection and upon withdrawing the needle, there was often back flux of fluid that was collected. At various times after injection the amount of radioactivity remaining in the brain was determined. The amount of radioactivity in the back flux and injection mixture was also determined. Radioactivity in brain was corrected for the back flux and the log of this corrected dpm was plotted against time. The $t_{½}$ was the inverse of the slope of the line multiplied by 0.301 (Banks et al., 1997).

To examine the role of P-gp and MRP , various substrates/inhibitors were co-administered with ^{14}C-AIT-082. The following substrates/inhibitors were used: a) probenecid: 350 mM in PBS containing 370 mM NaOH and 20 mM HCl, pH 7.4; b) verapamil: 200 mM in PBS containing 4.2% ethanol, pH 7.4; c) MK-571: 1, 10 or 100 mM in PBS. In all experiments the control group of animals was given ^{14}C-AIT-082 in PBS. Additionally, in experiments in which probenecid or verapamil were used, a second control group was given ^{14}C-AIT-082 in PBS containing 370 mM NaOH and 370 mM HCl, pH 7.4, or ^{14}C-AIT-082 in PBS with 4.2% ethanol, pH 7.4, respectively.

Intraparenchymal (ipc) Efflux Experiments

These experiments were conducted according the method of Banks et al. (1994) with minor modifications. Mice were anesthetized and then immobilized in a stereotaxic apparatus with a mouse adaptor coupled to a microinjection unit (Kopf, Tujunga, CA). A small hole was made in the skull with a Dremel drill (model 770; 2.4 mm drill bit, model 107) at -1 mm AP and 1 mm LL relative to Bregma. Using a guarded 0.5 μL Hamilton syringe (25 g), 0.1 μL PBS containing ^{14}C-AIT-082 (~5x10^4 dpm/μL) or ^{3}H-sucrose (~5x10^4 dpm/μL) was injected ipc at 3.5 min DV with respect to the skull. Back flux of injection fluid was collected and at various times after injection brains were removed. The amount of radioactivity in brain, back flux and injection mixture was measured. The amount of radioactivity in the brain was corrected for the back flux and the log of this corrected dpm was plotted against time. The $t_{½}$ was calculated as described above.

P-gp and MRP substrates/inhibitors were co-administered with ^{14}C-AIT-082 in the following concentrations: a) verapamil: 2 mM in water with less than 0.05% ethanol or 200 mM in water, 4% ethanol and 20 mM NaOH; b) MK-571: 10 mM in PBS. As above, all experiments included a control group in which ^{14}C-AIT-082 was administered in PBS. In the experiments in which verapamil was used, a second control group received ^{14}C-AIT-082 in water containing 4% ethanol and 20 mM NaOH.

Statistical Analysis

All data are presented as mean ± S.E. For comparisons of means from 2 groups an unpaired Student's t-test was used. For comparisons of means from 3 groups, ANOVA was performed coupled with Scheffe's post-hoc analysis.

Results

After both icv (Figure 1) and ipc (Figure 2) administration, ^{14}C-AIT-082 was transported out of brain in an exponential manner with a $t_{1/2}$ of 20 ± 1.0 and 35.0 ± 1.9 minutes, respectively. In both cases transport of ^{3}H-sucrose, a passively transported compound, was significantly slower (i.e. the $t_{1/2}$ was significantly higher). Administration of ^{14}C-AIT-082 icv exposes the compound to both the capillary endothelial cells and the choroid plexus epithelial cells of the blood-brain barrier. In contrast, when compounds are administered ipc, the endothelial cells are effectively isolated and efflux across this barrier can be examined. Thus, these data suggest that AIT-082 is transported out of brain by a saturable mechanism likely located at both the choroid plexus and brain capillary endothelium. This hypothesis was confirmed by the demonstration that excess unlabeled AIT-082 inhibited the efflux of ^{14}C-AIT-082 from brain after icv and ipc administration (Figure 3).

The role of P-gp and MRP in the transport of ^{14}C-AIT-082 out of brain was investigated. Verapamil, an inhibitor of P-gp, and both probenecid and MK-571, inhibitors of MRPs, significantly inhibited efflux of ^{14}C-AIT-082 after icv (Figure 4) and ipc administration (Figure 5). In addition, AIT-082 inhibited the efflux of ^{3}H-quinidine, a P-gp substrate, from brain after icv administration (Figure 6).

Conclusions: In conclusion, the data presented demonstrate that AIT-082 is transported out of brain by a saturable mechanism that is likely localized to both brain capillary endothelium and epithelium of the choroid plexus. The data indicate that P-gp and MRPs may mediate this efflux.

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ADVANTAGES OF THE INVENTION

The present invention provides new methods for treating diseases and conditions affected by activity of a multidrug transporter protein by inhibiting or modulating the activity of such a protein. These methods can be combined with methods that enable active compounds to bypass the blood-brain barrier, making combined therapy more efficient. These methods are suitable for use with a large variety of active compounds and should not depend on the specific interactions between each active compound and the transporter proteins. The methods of the invention are useful in treating malignancies, microbial and parasitic infections, HIV

infection, and conditions associated with inflammation, such as asthma and rheumatic disease. The invention provides particular advantages in treating malignancies, as it allows the use of smaller doses of potentially toxic anticancer agents, thus reducing the likelihood of side effects such as immune suppression.

Although the present invention has been described in considerable detail, with reference to certain preferred versions thereof, other versions and embodiments are possible. Therefore, the scope of the invention is determined by the following claims.

We claim:

1. A method of treating a disease or condition associated with the activity of a multi-drug transporter protein comprising administering to a patient suffering from a condition or disease associated with the activity of a multi-drug transporter protein an effective amount of a compound having activity against a multi-drug transporter protein, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L though a carbonyl group wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having activity against a multi-drug transporter protein; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

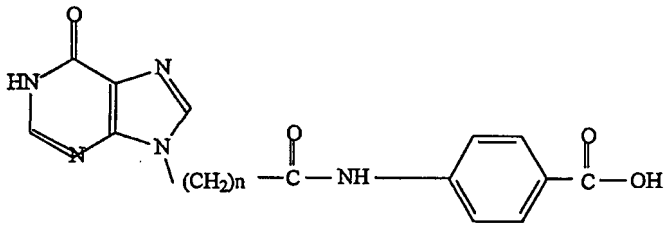
2. The method of claim 1 wherein the compound having activity against a multi-drug transporter protein passes through the blood-brain barrier.

3. The method of claim 1 wherein A is a purine moiety.

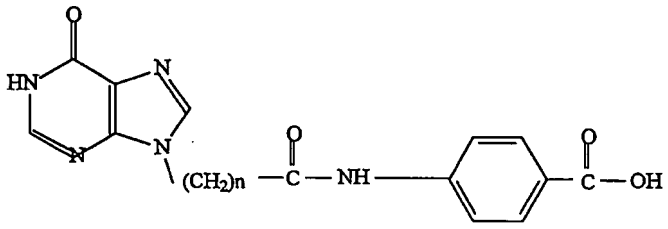
4. The method of claim 3 wherein A is a substituted or unsubstituted hypoxanthine moiety.

5. The method of claim 4 wherein L has the structure $–(CH_2)_n$-CONH- where n is an integer from 1 to 6.

6. The method of claim 5 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (I)



where n is an integer from 1 to 6 and R is hydrogen or lower alkyl or is a salt or prodrug ester of a compound of formula (I)



wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl.

7. The method of claim 6 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (I) wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl.

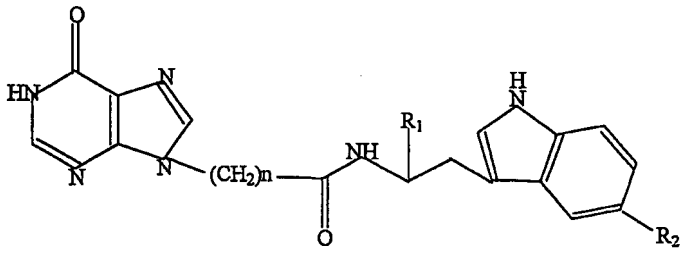
8. The method of claim 7 wherein R is hydrogen.

9. The method of claim 8 wherein n is 2 and the compound is N-4-[[3-(1,6-dihydro-6-oxo-purin-9-yl)-1-oxopropyl] amino] benzoic acid.

10. The method of claim 7 wherein R is ethyl.

11. The method of claim 10 wherein n is 2 and the compound is N-4-[[3-(1,6-dihydro-6-oxo-purin-9-yl)-1-oxopropyl] amino] benzoic acid ethyl ester.

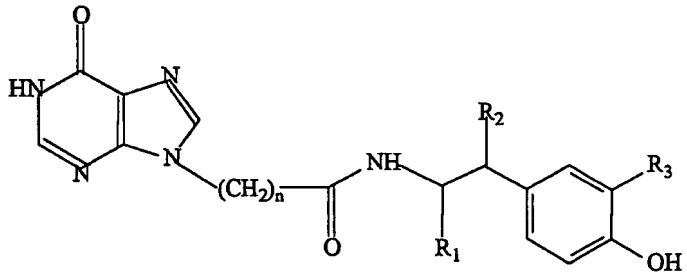
12. The method of claim 5 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (II)



wherein n is an integer from 1 to 6, R is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, and R_2 is selected from the group consisting of H and OH.

13. The method of claim 12 wherein n is 2.

14. The method of claim 5 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (III)



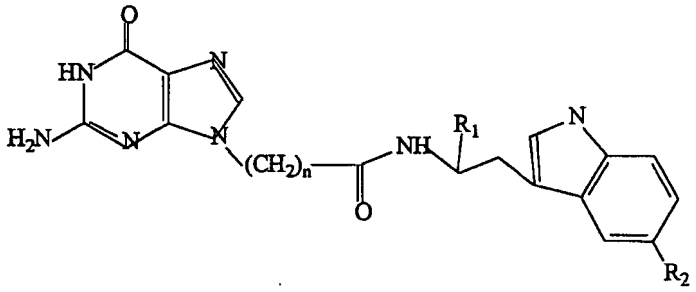
wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting from the group consisting of H and OH.

15. The method of claim 14 wherein n is 2.

16. The method of claim 3 wherein A is a substituted or unsubstituted guanine moiety.

17. The method of claim 16 wherein L has the structure $-(CH_2)_n$-CONH- wherein n is an integer from 1 to 6.

18. The method of claim 17 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (IV)



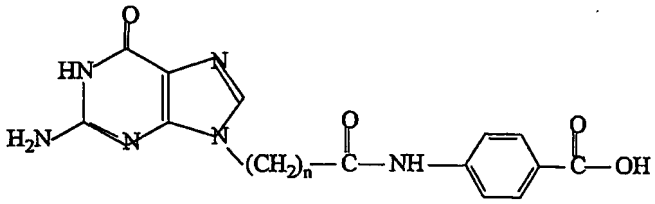
wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino and R_2 is selected from the group consisting of H and OH.

19. The method of claim 18 wherein n is 2, R_1 is H, and R_2 is OH, and the compound is N-(2-(5-hydroxyindol-3-yl)) ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

20. The method of claim 18 wherein n is 2, R_1 is H, and R_2 is H, and the compound is N-(2-(2-indol-3-yl)ethyl))-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

21. The method of claim 18 wherein n is 2, R_1 is COOH, and R_2 is OH, and the compound is N-(1-carboxyl-(2-(5-hydroxyindol-3-yl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

22. The method of claim 17 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (V)

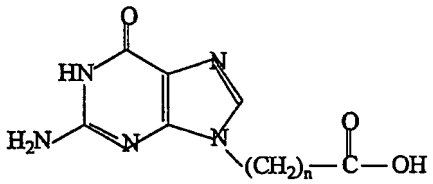


wherein n is an integer from 1 to 6 and R is selected from the group consisting of hydrogen and lower alkyl.

23. The method of claim 22 wherein n is 2, R is hydrogen, and the compound is N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

24. The method of claim 22 wherein n is 2, R is ethyl, and the compound is N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide ethyl ester.

25. The method of claim 17 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (VI)

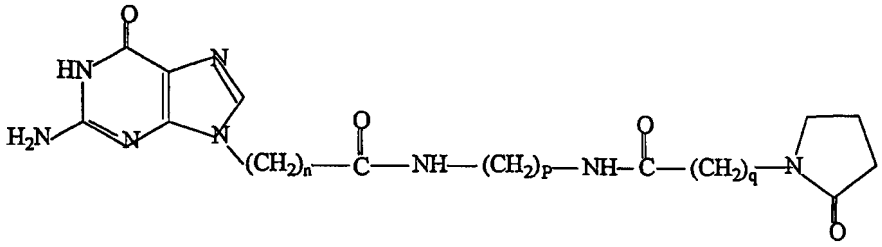


wherein n is an integer from 1 to 6 and R is selected from the group consisting of hydrogen and lower alkyl.

26. The method of claim 25 wherein n is 2, R is hydrogen, and the compound is 3-(2-amino-6-oxohydropurin-9-yl) propanoic acid.

27. The method of claim 25 wherein n is 2, R is ethyl, and the compound is 3-(2-amino-6-oxohydropurin-9-yl) propanoic acid ethyl ester.

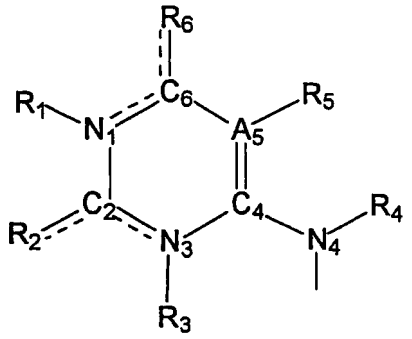
28. The method of claim 17 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (VII)



wherein n is an integer from 1 to 6, p is an integer from 1 to 6, and q is an integer from 1 to 3.

29. The method of claim 28 wherein n is 2, p is 2, and q is 1, and the compound is N-[2-[[2-(2-oxopyrrolidin-1-yl)-1-oxoethyl] amino] ethyl] propanamide.

30. The method of claim 17 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (VIII)



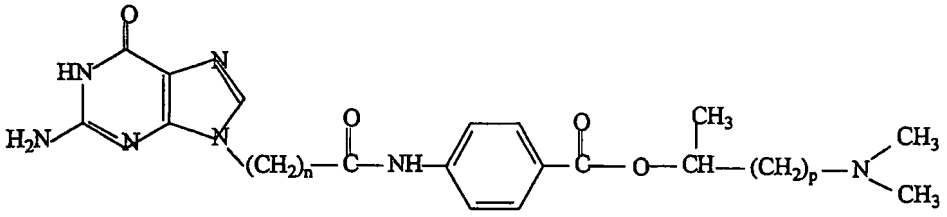
wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting of H and OH.

31. The method of claim 30 wherein n is 2, R_1 is H, R_2 is H, and R_3 is OH, and the compound is N-(2-(3,4-dihydroxyphenyl)ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

32. The method of claim 30 wherein n is 2, R_1 is H, R_2 is OH, and R_3 is OH, and the compound is N-(2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

33. The method of claim 30 wherein n is 2, R_1 is COOH, R_2 is H, and R_3 is H, and the compound is N-(1-carboxyl-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

34. The method of claim 16 wherein the compound having activity against a multi-drug transporter protein is a compound of formula (IX)

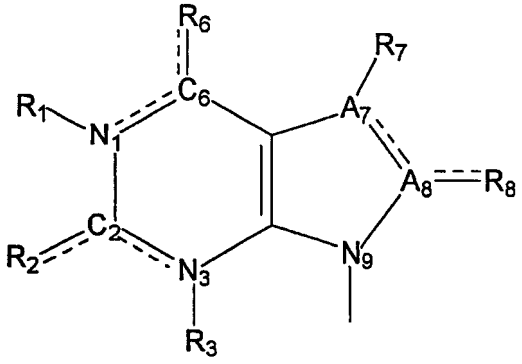


wherein n is an integer from 1 to 6 and p is an integer from 1 to 3.

35. The method of claim 34 wherein n is 2, p is 1, and the compound is N-4-[[3-(2-amino-6-oxohydropurin-9-yl) 1-oxopropyl] amino] benzoic acid 1-(dimethylamino)-2-propyl ester.

36. The method of claim 1 wherein A is a substituted or unsubstituted 9-atom bicyclic moiety in which the 5-membered ring has 1 to 3 nitrogen atoms, the

bicyclic moiety having the structure of formula (X)



where:

(a) if the bond between N_1 and the bond between C_5 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(b) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(c) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(d) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1,

where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(e) A_7 and A_8 are C or N;

(i) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a single bond, then the bond between A_8 and R_8 is two single bonds to two hydrogen atoms or is a double bond in which R_8 is O or S and R_7 is two hydrogen atoms;

(ii) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a double bond, then R_7 is hydrogen, the bond between A_8 and R_8 is a single bond and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(iii) if A_7 and A_8 are both N, then the bond between A_7 and A_8 is a double bond, and R_7 and R_8 are not present;

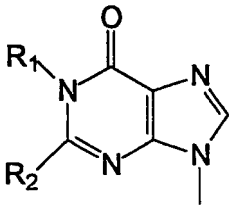
(iv) if A_7 is C and A_8 is N, then the bond between A_7 and A_8 is a double bond, R_7 is hydrogen, and R_8 is not present;

(v) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a double bond, then R_7 is not present, the bond between A_8 is a single bond, and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(vi) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a single bond, then R_7 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, the bond between A_8 and R_8 is a double bond, and R_8 is O or S; and

(f) N_9 is bonded to L; with the proviso that A does not have the structure of an unsubstituted guanine or hypoxanthine.

37. The method of claim 3 wherein the purine moiety is a purine moiety of formula (XI)



in which:

(a) R_1 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, and heteroaralkyl; and R_2 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylokoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroarylkylaminocarbonyl in which the alkyl portions could be cyclic and can contain from one to three heteroatoms which could be N, O, or S, with the proviso that both R_1 and R_2 are not hydrogen and that R_1 is not hydrogen when R_2 is amino.

38. The method of claim 37 wherein R_1 is butyl and R_2 is hydrogen.

39. The method of claim 37 wherein R_1 is benzyl and R_2 is hydrogen.

40. The method of claim 37 wherein R_1 is dimethylaminoethyl and R_2 is hydrogen.

41. The method of claim 37 wherein R_1 is cyclopentyl and R_2 is hydrogen.

42. The method of claim 37 wherein R_1 is cyclohexylmethyl and R_2 is hydrogen.

43. The method of claim 37 wherein R_1 is cyclopropylmethyl and R_2 is hydrogen.

44. The method of claim 37 wherein R_1 is hydrogen and R_2 is phenyl.

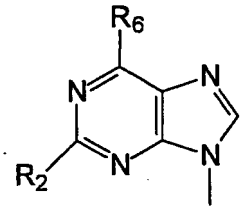
45. The method of claim 37 wherein R_1 is hydrogen and R_2 is butyl.

46. The method of claim 37 wherein R_1 is butyl and R_2 is butyl.

47. The method of claim 37 wherein R_1 is hydrogen and R_2 is methyl.

48. The method of claim 37 wherein R_1 is hydrogen and R_2 is phenylamino.

49. The method of claim 3 wherein the purine moiety is a purine moiety of Formula (XII)



in which:

(a) R_2 is selected from the group consisting of hydrogen, halo, amino, OQ_3, SQ_3, $NHNH_2$, $NHOQ_3$, NQ_3Q_4, or NHQ_3, where Q_3 and Q_4 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_3 and Q_4 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3 where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(b) R_6 is selected from the group consisting of hydrogen, halo, amino, OQ_5, SQ_5, $NHNH_2$, $NHOQ_5$, NQ_5Q_6, or NHQ_6, where Q_5 and Q_6 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_5 and Q_6 are present together and are alkyl, they can be taken together to form a 5- or 6- membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

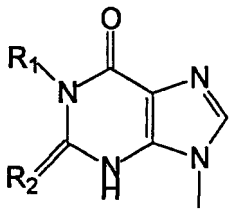
50. The method of claim 49 wherein R_2 is hydrogen and R_6 is amino.

51. The method of claim 49 wherein R_6 is chloro.

52. The method of claim 49 wherein R_6 is phenylamino.

53. The method of claim 49 wherein R_2 is amino and R_6 is chloro.

54. The method of claim 3 wherein the purine moiety is a purine moiety of Formula (XIII)



in which:

(a) R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl; and

(b) R_2 is O or S.

55. The method of claim 54 wherein R_1 is hydrogen.

56. The method of claim 54 wherein R_2 is O.

57. The method of claim 54 wherein R_2 is S.

58. The method of claim 3 wherein the compound is 4-[3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester.

59. The method of claim 3 wherein the compound is 4-[3-(1-butyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester.

60. The method of claim 3 wherein the compound is 4-[3-(1-methyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester.

61 The method of claim 3 wherein the compound is 4-[3-(1-2-dimethylaminoethyl)-6-oxo-1,6-dihydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

62. The method of claim 3 wherein the compound is 4-[3-(2,6-dioxo-1,2,3,6-tetrahydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

63. The method of claim 3 wherein the compound is 4-[3-(6-methoxypurin-9-yl) propionylamino] benzoic acid ethyl ester.

64. The method of claim 3 wherein the compound is 4-[3-(6-dimethylaminopurin-9-yl) propionylamino] benzoic acid ethyl ester.

65. The method of claim 3 wherein the compound is 4-[3-(2-amino-6-chloropurin-9-yl) propionylamino] benzoic acid ethyl ester.

66. The method of claim 3 wherein the compound is 4-[2-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

67. The method of claim 3 wherein the compound is 4-[2-(2-butyl-6-oxo-1,6-dihydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

68. The method of claim 3 wherein the compound is 4-[2-(6-oxo-2-phenyl-1,6-dihydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

69. The method of claim 3 wherein the compound is 4-{[3-(6-chloropurin-9-yl) propionyl] methylamino} benzoic acid methyl ester.

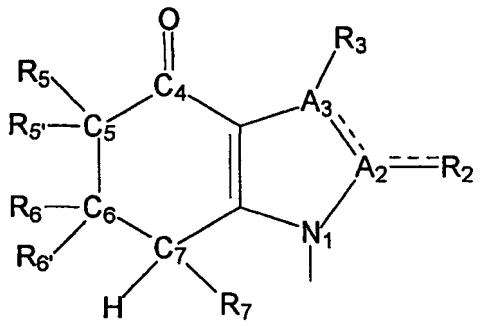
70. The method of claim 3 wherein the compound is 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-[3-(2-oxopyrrolidin-1-yl)propyl] propanamide.

71. The method of claim 3 wherein the compound is 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-{2-[2-(2-oxopyrrolidin-1-yl)acetylamino]ethyl} propanamide.

72. The method of claim 3 wherein the compound is N-[3-(2-oxopyrrolidin-1-yl)propyl]-3-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl) propanamide.

73. The method of claim 3 wherein the compound is 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-(3-morpholin-4-yl)propyl propionamide.

74. The method of claim 1 wherein the compound is a tetrahydroindolone derivative or analogue where A is a 9-atom bicyclic moiety in which the 5-membered ring has one to three nitrogen atoms, the bicyclic moiety of Formula (XIV)



where:

(a) N_1 is bonded to L;

(b) A_2 and A_3 are C or N;

(i) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a single bond, then the bond between A_2 and R_2 is two single bonds, two hydrogen atoms or is a double bond in which R_2 is O or S and R_3 is two hydrogen atoms;

(ii) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a double bond, then R_3 is hydrogen, the bond between A_2 and R_2 is a single bond and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(iii) If A_2 and A_3 are both N, then the bond between A_2 and A_3 is a double bond and R_2 and R_3 are not present;

(iv) If A_2 is N and A_3 is C, then the bond between A_2 and A_3 is a double bond, R_2 is not present, and R_3 is hydrogen;

(v) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a double bond, then R_3 is not present, the bond between A_2 and R_2 is a single bond, and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(vi) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a single bond, then R_3 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkenyl, the bond between A_2 and R_2 is a double bond, and A_2 is O or S;

(c) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHQ_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(d) $R_{5'}$ is hydrogen unless R_5 is alkyl, in which case R_5 is hydrogen or the same alkyl as R_5;

(e) R_5 and $R_{5'}$ can be taken together as a double bond to C_5, and can be O, S, NQ_3, or C which can be substituted with one or two groups R_5, where Q_3 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(f) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, NH_2, NHQ_4, NQ_4Q_5, OH, OQ_4, or SQ_4, where Q_4 and Q_5 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl,

alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_4 and Q_5 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

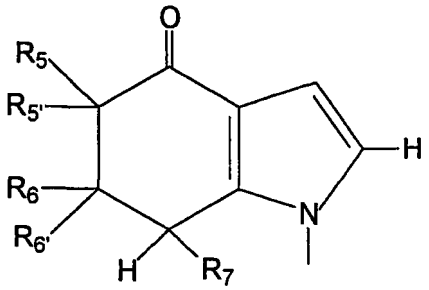
(g) $R_{6'}$ is hydrogen unless R_6 is alkyl, in which case $R_{6'}$ is hydrogen or the same alkyl as R_6;

(h) R_6 and $R_{6'}$ can be taken together as a double bond to C_6 and can be O, S, NQ_6, or C which can be substituted with one or two groups R_5, and where Q_6 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(i) R_7 is hydrogen unless R_5 is alkyl and $R_{5'}$ is hydrogen, in which case R_7 is the same alkyl as R_5.

75. The method of claim 74 wherein A is a tetrahydroindolone moiety.

76. The method of claim 75 wherein the tetrahydroindolone moiety is a tetrahydroindolone moiety of formula (XV)



in which:

(a) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NH_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

(b) $R_{5'}$ is hydrogen;

(c) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHW_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S and where W_1 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

(d) $R_{6'}$ is hydrogen; and

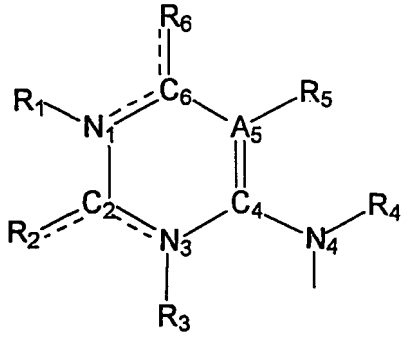
(e) R_7 is hydrogen.

77. The method of claim 76 wherein R_5, $R_{5'}$, R_6, $R_{6'}$, and R_7 are all hydrogen.

78. The method of claim 77 wherein the compound is 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid ethyl ester.

79. The method of claim 77 wherein the compound is 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid.

80. The method of claim 1 wherein A is an amino-substituted 6-membered heterocyclic moiety of formula (XVI)



where:

(a) if the bond between N_1 and the bond between C_6 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(b) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(c) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(d) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 and R_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl,

aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3, where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(e) R_4 is hydrogen, alkyl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl;

(f) A_5 is carbon or nitrogen;

(g) if A_5 is nitrogen, then R_5 is not present;

(h) if A_5 is carbon, then R_5 is hydrogen, amino, alkyl, alkoxy, halo, nitro, aryl, cyano, alkenyl, or alkaryl;

(i) if R_5 and R_6 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(j) N_4 is bonded to L.

81. The method of claim 80 wherein A_5 is carbon and the 6-membered heterocyclic moiety is a pyrimidine moiety.

82. The method of claim 81 wherein R_2 is O and R_3 is hydrogen.

83. The method of claim 82 wherein the pyrimidine moiety is selected from the group consisting of cytosine, thymine, uracil, 3-methyluracil, 3-methylthymine, 4-methylcytosine, 5-methylcytosine, 5-hydroxymethylcytosine, 5-hydroxyuracil, 5-carboxymethyluracil, and 5-hydroxymethyluracil.

84. The method of claim 81 wherein R_2 is S and R_3 is hydrogen.

85. The method of claim 84 wherein the pyrimidine moiety is selected from the group consisting of 2-thiouracil, 5-methylamino-2-thiouracil, 5-methyl-2-thiouracil, 2-thiocytosine.

86. The method of claim 81 wherein R_2 is amino and the bond between C_2 and N_3 is a double bond.

87. The method of claim 86 wherein the pyrimidine moiety is selected from the group consisting of 2-aminopyrimidinone and 2-amino-4-chloropyrimidine.

88. The method of claim 81 wherein R_2 is hydrogen and the bond between C_2 and N_3 is a double bond.

89. The method of claim 88 wherein the pyrimidine moiety is selected from the group consisting of 4-chloropyrimidine, 5-amino-4-chloropyrimidine, 4-chloro-5-methylpyrimidine, 4-chloro-5-hydroxymethylpyrimidine, and 4-chloro-5-carboxymethylpyrimidine.

90. The method of claim 81 wherein R_1 is hydrogen, methyl, or ethyl, R_5 is hydrogen, methyl, or ethyl, and R_6 is O.

91. The method of claim 90 wherein the pyrimidine moiety is pyrimidinone.

92. The method of claim 81 wherein the compound is 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

93. The method of claim 81 wherein the compound is 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

94. The method of claim 81 wherein the compound is 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

95. The method of claim 81 wherein the compound is 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

96. The method of claim 81 wherein the compound is 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

97. The method of claim 81 wherein the compound is 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

98. The method of claim 81 wherein the compound is 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

99. The method of claim 81 wherein the compound is 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

100. The method of claim 81 wherein the compound is 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

101. The method of claim 81 wherein the compound is 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

102. The method of claim 81 wherein the compound is 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

103. The method of claim 81 wherein the compound is 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

104. The method of claim 1 wherein L has the structure $-(CH_2)_n-$ wherein n is an integer from 1 to 6.

105. The method of claim 104 wherein n is 2.

106. The method of claim 104 wherein n is 3.

107. The method of claim 1 wherein the moiety B is –OZ.

108. The method of claim 107 wherein Z is hydrogen.

109. The method of claim 107 wherein Z is alkyl.

110. The method of claim 109 wherein Z is selected from the group consisting of methyl, ethyl, butyl, propyl, and isopropyl.

111. The method of claim 1 wherein B is $-N(Y_1)-D$.

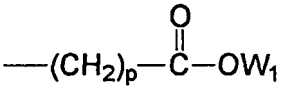
112. The method of claim 111 wherein Y_1 is hydrogen.

113. The method of claim 111 wherein Y_1 is lower alkyl.

114. The method of claim 113 wherein Y_1 is methyl.

115. The method of claim 111 wherein D is a moiety having at least one polar, charged, or hydrogen-bond-forming group to increase the water-solubility of the compound.

116. The method of claim 115 wherein D is a carboxylic acid or carboxylic acid ester with the structure

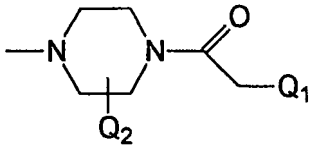


wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of hydrogen and lower alkyl.

117. The method of claim 116 wherein W_1 is hydrogen.

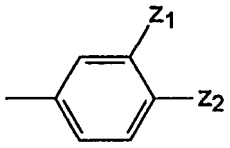
118. The method of claim 116 wherein W_1 is ethyl.

119. The method of claim 115 wherein D and Y_1 are taken together to form a piperazine derivative of the structure



wherein Q_1 is hydrogen, methyl, ethyl, butyl, or propyl, and Q_2 is hydrogen or methyl, where, if Q_2 is methyl, it can be located on either of the two possible positions in the piperazine ring.

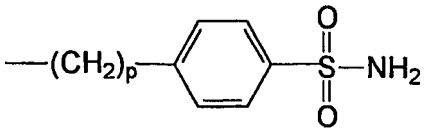
120. The method of claim 115 wherein D has the structure



wherein one of Z_1 and Z_2 is hydrogen and the other is Z_1 and Z_2 is –COOH or –$COOW_1$, wherein W_1 is alkyl.

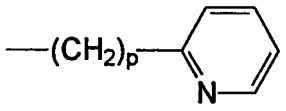
121. The method of claim 120 wherein W_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, and isobutyl.

122. The method of claim 115 wherein D is a phenylsulfonamidyl moiety of the structure



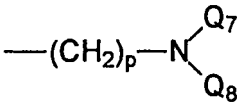
wherein p is an integer from 0 to 6.

123. The method of claim 115 wherein D is an alkylpyridyl moiety of the structure



wherein p is an integer from 1 to 6.

124. The method of claim 114 wherein D is an dialkylaminoalkyl moiety of the structure



wherein p is an integer from 1 to 6 and Q_7 and Q_8 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_7 and Q_8 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

125. The method of claim 124 wherein Q_7 and Q_8 are each alkyl.

126. The method of claim 125 wherein Q_7 and Q_8 are each selected from the group consisting of methyl, ethyl, propyl, butyl, and isobutyl.

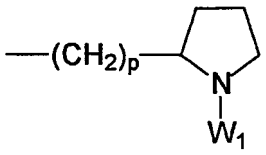
127. The method of claim 126 wherein Q_7 and Q_8 are taken together to form 5- or 6-membered optionally substituted ring.

128. The method of claim 127 wherein the ring is a morpholinyl ring.

129. The method of claim 127 wherein the ring is a pyrrolidinyl ring that is optionally substituted with oxo.

130. The method of claim 126 wherein the ring is a piperidinyl ring that is optionally substituted with methyl or ethyl.

131. The method of claim 115 wherein D is an alkylpyrrolidinyl moiety of the structure



wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of methyl, ethyl, and propyl.

132. The method of claim 1 wherein the compound has a log P of from about 1 to about 4.

133. The method of claim 1 wherein the multidrug transporter protein is selected from the group consisting of P-glycoprotein and multidrug resistance associated proteins (MRPs).

134. The method of claim 133 wherein the multidrug transporter protein is P-glycoprotein.

135. The method of claim 133 wherein the multidrug transporter protein is MRP.

136 The method of claim 1 wherein the condition or disease associated with the activity of a multidrug transporter protein is selected from the group consisting of cancer, a microbial or parasitic infection, HIV infection, and a condition associated with inflammation.

137. The method of claim 136 wherein the condition or disease is cancer.

138. The method of claim 136 wherein the condition or disease is a microbial or parasitic infection.

139. The method of claim 136 wherein the condition or disease is a HIV infection.

140 The method of claim 136 wherein the condition or disease is a condition associated with inflammation.

141. The method of claim 140 wherein the condition associated with inflammation is selected from the group consisting of asthma and rheumatic disease.

142. A method of increasing intestinal absorption of a drug transported by a multi-drug transporter protein comprising administering to a mammal an effective amount of a compound having activity against a multi-drug transporter protein, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having activity against a multi-drug transporter protein; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

143. A method of improving the penetration of a drug transported by a multi-drug transporter into the central nervous system comprising administering to a mammal an effective amount of a compound having activity against a multi-drug transporter protein, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower

alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having activity against a multi-drug transporter protein; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

144. A method of decreasing renal excretion or renal toxicity of a drug transported by a multi-drug transporter protein comprising administering to a mammal an effective amount of a compound having activity against a multi-drug transporter protein, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having activity against a multi-drug transporter protein; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

145. A method of treating a malignancy comprising:

(a) administering an effective quantity of an antineoplastic agent transported by a multidrug transporter protein to a mammal with cancer; and

(b) administering an effective amount of a compound having activity against a multi-drug transporter protein, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having activity against a multi-drug transporter protein; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

146. The method of claim 145 wherein the antineoplastic agent is selected from the group consisting of adriamycin, etoposide, vinblastine, actinomycin D, and taxol.

147. A method for screening a compound for the existence or nonexistence of multidrug resistance transporter protein inhibitory activity comprising the steps of:

(a) adding the compound to a culture of cancer cells that constitutively express or are induced to express at least one multidrug resistance transporter protein;

(b) adding a cytotoxic agent transported by the multidrug resistance transport protein to the cells;

(c) determining the effect of the compound on the activity of the multidrug resistance transporter protein by performing one or both of a cytotoxicity assay and a drug accumulation assay on the cancer cells to measure either the

cytotoxicity of the cytotoxic agent or the accumulation of the cytotoxic agent in the cancer cells; and

(d) comparing the effect of the compound on the activity of the multidrug transporter protein with the effect of a reference compound, N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide.

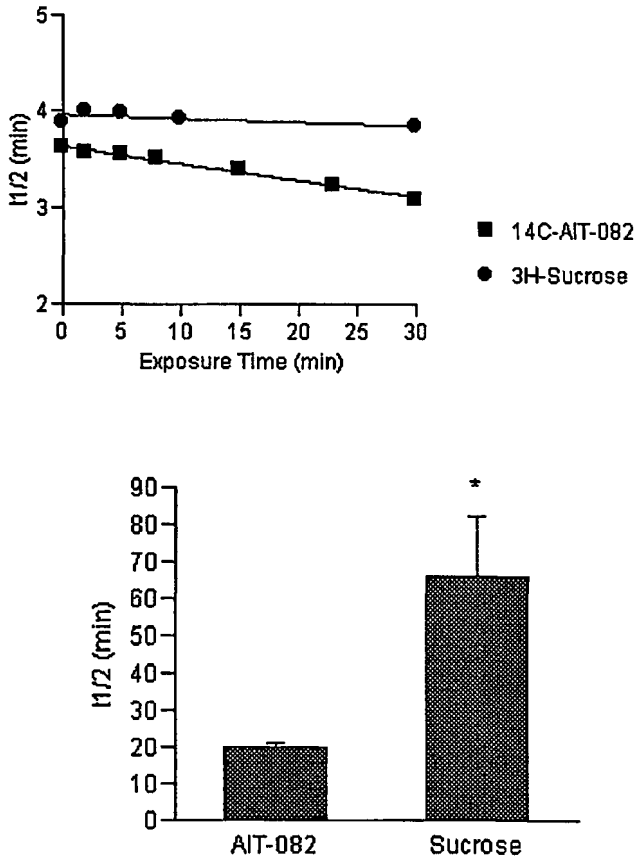

5
4
3
2
t1/2 (min)
0
5
10
15
20
25
30
Exposure Time (min)
14C-AIT-082
3H-Sucrose
90
80
70
60
50
40
30
20
10
0
t1/2 (min)
*
AIT-082
Sucrose

FIG. 1

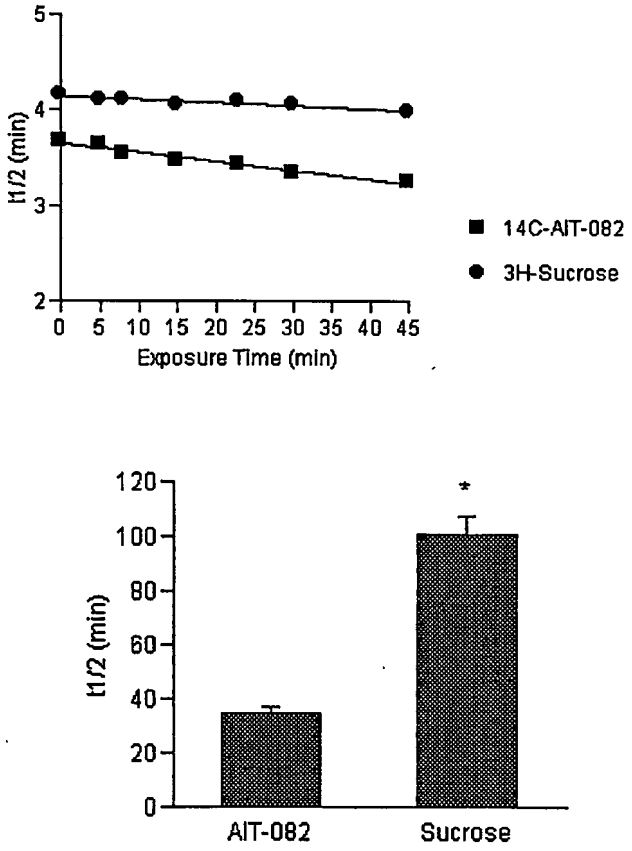

5
4
3
2
t1/2 (min)
0 5 10 15 20 25 30 35 40 45
Exposure Time (min)
14C-AIT-082
3H-Sucrose
120
100
80
60
40
20
0
t1/2 (min)
*
AIT-082
Sucrose

FIG. 2

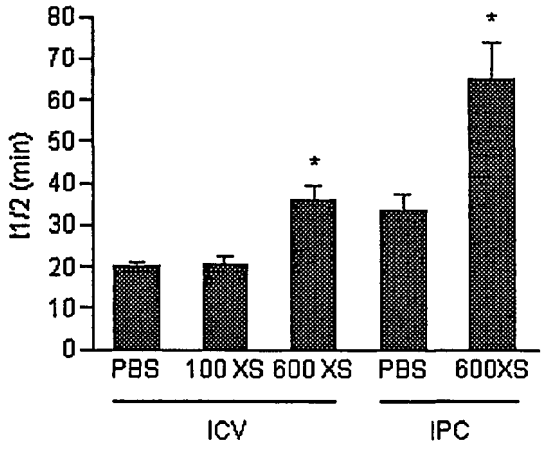

t1/2 (min)
80
70
60
50
40
30
20
10
0
*
*
PBS
100 XS
600 XS
PBS
600XS
ICV
IPC

FIG. 3

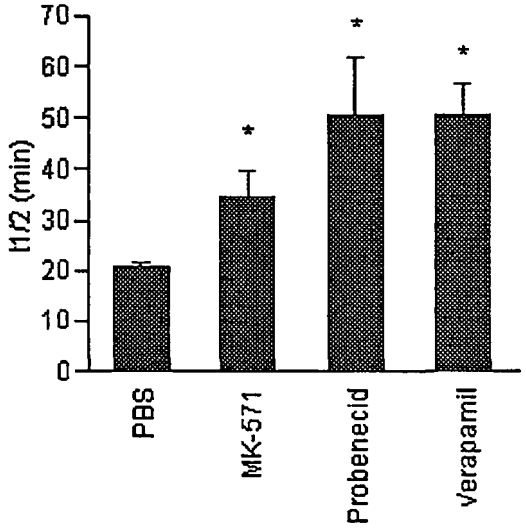

t1/2 (min)
70
60
50
40
30
20
10
0
*
*
*
PBS
MK-571
Probenecid
Verapamil

FIG. 4

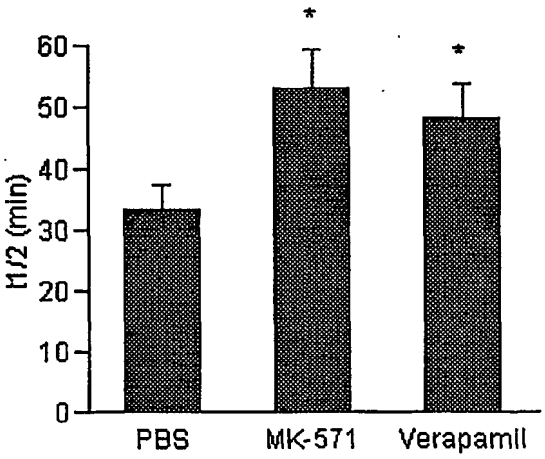

t1/2 (min)
60
50
40
30
20
10
0
*
*
PBS
MK-571
Verapamil

FIG. 5

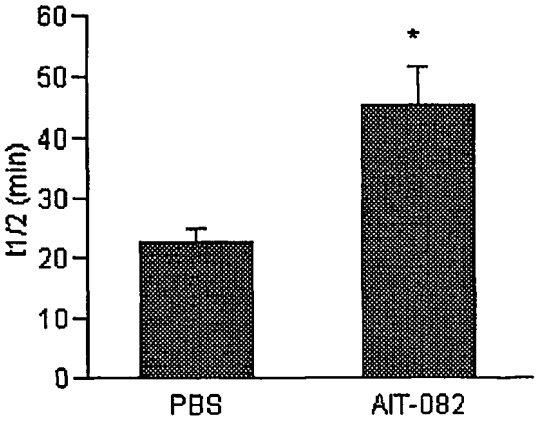

t1/2 (min)
60
50
40
30
20
10
0
*
PBS
AIT-082

FIG. 6